Implementation of Pharmacogenetics - The PriME-PGx Initiative

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Pharmacogenetics is the medical discipline born in the 1950s that studies the role of genetic variation affecting drug response or adverse reactions to drugs. Implemented in the clinical practice, this discipline helps to bring a personalized treatment to each patient. Consequently, ineffective or potentially toxic treatments are avoided or optimized. Here, we present the experience in Clinical Pharmacogenetics Implementation at the Clinical Pharmacology Department, Hospital Universitario de La Princesa.

Keywords: clinical pharmacogenetics ; implementation ; precision medicine ; personalized treatment

1. Introduction

Pharmacogenetics is the medical discipline born in the 1950s that studies the role of genetic variation affecting drug response or adverse reactions to drugs [1]. Implemented in the clinical practice, this discipline helps to bring a personalized treatment to each patient. Consequently, ineffective or potentially toxic treatments are avoided or optimized. Unfortunately, during the past decades, the implementation of pharmacogenetics in clinical practice was limited for various reasons. Firstly, the lack of consistency in clinical recommendations and of the usefulness of pharmacogenetics. Secondly, the budgetary constraints that impeded routine large-scale genotyping of patients. Thirdly, the difficulty of interpreting pharmacogenetic information or the lack of specialists in the field. Fourthly, the lack of training of prescribing physicians and pharmacists, which made them hesitant to trust this discipline. However, by 2020, the situation was very different: there were several clinical pharmacogenetic guidelines from different scientific societies or consortia, some of them with very high levels of evidence. These include the Consortium for the Implementation of Clinical Pharmacogenetics (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), among others, who base their clinical recommendations on a comprehensive compilation of scientific evidence. Moreover, the cost of genetic testing was significantly reduced; for instance, the complete sequencing of the human genome was worth approximately 100 million dollars in 2001, whereas nowadays it costs approximately 600 dollars [2]. Nowadays, specialists in pharmacogenetics capable of interpreting the clinical guidelines have been trained and are able to give sound therapeutic recommendations. As a consequence, physicians and pharmacists are nowadays much more willing to apply pharmacogenetics in the management of patients. Furthermore, the pharmacoeconomic repercussion of pharmacogenetics implementation in the clinical practice has been studied widely; in conclusion, most pharmacogenetic tests are cost-effective or cost-saving [3][4][5][6]; nevertheless, in some therapeutic areas, further studies are required to determine cost-effectiveness [7].

The Clinical Pharmacology Department of Hospital Universitario de La Princesa (Madrid, Spain) is promoting an initiative for the implementation of pharmacogenetics: La Princesa University Hospital Multidisciplinary Initiative for the Implementation of Pharmacogenetics (PriME-PGx). Our initiative is not the first one to promote a similar action. Other initiatives, mainly from the United States, are active nowadays or finished recently. To our understanding, in Spain, the first and only implementation initiative is the MedeA initiative [8]. Briefly, this initiative intends to “integrate pharmacogenetics and other relevant information in a decision supporting tool to be used for individualized drug prescription during regular clinical practice within the context of e-health”. Our initiative is the second one of this kind in Spain and the third in Europe after the one promoted by the Ubiquitous Pharmacogenomics Consortium (U-PGx) [9]. The latter has not finished yet (ClinicalTrials.gov identifier NCT03093818). Nevertheless, the PriME-PGx initiative is novel and of great interest as it promotes the expansion of pharmacogenetics in the Hospital’s patients, in the general population and in the field of clinical trials; later in this text, it will be thoroughly described. However, to provide a context, in the following paragraphs some important implementation initiatives are described. van der Wouden et al. , on behalf of the U-PGx, reviewed implementation projects and initiatives promoted over recent years [9], which are summarized as follows:

There are several other noteworthy initiatives: IGNITE (University of Florida, Indiana and Vanderbilt, USA), INGENIOUS (Indiana Institute of Personalized Medicine, USA), Personalized Medicine Program (University of Florida and Shands Hospital, USA), PG4KDS (St. Jude Children's Research Hospital, USA), PGRN (University of Maryland, Florida, St Jude Children's Hospital, among others), PREDICT (Vanderbilt University Medical Center, USA), RIGHT (Mayo Clinic, USA), The 1200 Patients Project (University of Chicago, USA), the Sanford Chip (Stanford Imagenetics Initiative, available at: genomes2people.org, accessed on 12 August 2021) [10], the implementation initiative of University of Colorado's Biobank [11], among others. Furthermore, Borobia et al., from Hospital Universitario de La Paz, Madrid (Spain) published in 2018 their experience in clinical pharmacogenetics implementation [12]. Other projects have promoted the creation of other clinical decision support system (CDSS) tools to help with the integration of pharmacogenetic information in the clinical context, such as the FARMAPRICE CDSS and several others [13][14][15][16][17]. These were thoroughly revised by Hinderer et al. [18].

The constitution of the above-mentioned initiatives and our experience in clinical pharmacogenetics encouraged us to summarize our assistance activity since the constitution of our Pharmacogenetics Unit. Furthermore, we are currently promoting two novel sub-projects within the scope of the PriME-PGx initiative. As will be mentioned below, our project has some strengths and novelties compared to previous works. On the one hand, the historical achievements since the creation of our group are described, as well as the technological advances and milestones accomplished. On the other hand, the two mentioned starting ongoing sub-projects are presented: the PROFILE and the GENOTRIAL projects.

2. Historical Achievements

Founded in April 1857, the Hospital Universitario de La Princesa is a University Hospital of Madrid's Health Service, Spain, that assists 323,000 people for basic specialties, and is the reference Hospital for nearly one million for highly complex specialties, such as neurosurgery, cardiac surgery, or thoracic surgery, among others. Annually, 16,000 hospital admissions are attended; 440,000 outpatients and 100,000 emergency patients are assisted. In 2018, the 2000th bone marrow transplant took place. The Clinical Pharmacology Department was established in 1995, thanks to the promotion of the Pharmacology department of Universidad Autónoma de Madrid. It offers the following healthcare services: therapeutic drug monitoring (TDM) (e.g., for antipsychotics and tyrosine kinase inhibitors, among others), general therapeutic consultations, Pain Management Unit consultations, evaluation of clinical study protocols, assistance in clinical trial design, promotion and performance, assistance in the evaluation of new drugs, medication errors, pharmacovigilance (i.e., adverse event reporting), and pharmacogenetics. Likewise, the Clinical Trials Unit of Hospital Universitario de La Princesa (UECHUP), part of the Clinical Pharmacology Department and of the PriME-PGx initiative, performs more than 20 clinical trials per year, ensuring a valuable source of data for pharmacogenetic research.

In the absence of recommendations from a Spanish society or consortium on pharmacogenetics, we initially adhered solely to CPIC pharmacogenetic guidelines [19][20]. With the progression of the discipline, other relevant societies emerged with clinical guidelines. Since 2017, for gene-drug pairs where CPIC has no guideline, the Dutch Pharmacogenetics Working Group (DPWG) recommendations [21] are applied. Should there be discrepancies between CPIC and DPWG recommendations for a particular drug-gene association, our consensus is to adhere to the CPIC recommendations. Furthermore, nowadays, some pharmacogenetic information is issued by regulatory agencies for certain drugs; in our case, AEMPS/EMA drug labels are fully addressed.

The portfolio of available tests changed over these years as we were able to overcome some of the above-mentioned barriers: our genotyping capacity was significantly improved and became more cost-effective: nowadays, we conduct array-based genotyping; the Spanish regulator (AEMPS) issued several genotyping recommendations (e.g., for siponimod and CYP2C9 or for fluoropyrimidines and DPYD); and physicians and pharmacists are more aware of the usefulness of pharmacogenetics.

Table 1 shows all the genes included in our custom genotyping array (the Very Important Pharmacogene Open Array panel, VIPOA) with available clinical prescribing information and some of the important variants used to infer enzyme phenotype. Since CPIC provides comprehensive allele definition tables, functionality tables, etc. , CPIC guidance, which is linked to PharmVAR, is followed in our pharmacogenetic unit. Consequently, all alleles considered "actionable" included in our array are described in CPIC/PharmVAR. Nevertheless, not all the variants in our array are clinically actionable (i.e., related to a pharmacogenetic phenotype that would require a modification of routine practice).

Table 1. Genes and variants included in the VIPOA genotyping panel.

Gene	Allele	SNP (rs)	Ancestral	Mutant	Defines Actionable [#1] Allele?
CYP4F2	Not defined	rs2108622	C	T	YES
CYP2B6	Multiple	rs3745274	G	T	YES
	Multiple	rs3211371	C	T	YES
	Not defined	rs4803419	C	T	NO
	Multiple	rs2279343	A	G	YES
	*22	rs34223104	C	T	YES
	*18, *16	rs28399499	T	C	YES
CYP2C9	*2	rs1799853	C	T	YES
	*3	rs1057910	A	C	YES
	*5	rs28371686	C	G	YES
	*8	rs9332094	T	C	YES
	*8	rs7900194	T	G	YES
	*11	rs28371685	C	T	YES
CYP2C19	*2	rs4244285	G	A	YES
	*3	rs4986893	G	A	YES
	*4	rs28399504	A	G	YES
	*6	rs72552267	G	A	YES
	*5	rs56337013	C	T	YES
	*7	rs72558186	T	C	YES
	*8	rs41291556	T	C	YES
	*9	rs17884712	G	A	YES
	*17	rs12248560	C	T	YES
	*2, *35	rs12769205	A	G	YES

Gene	Allele	SNP (rs)	Ancestral	Mutant	Defines Actionable [#1] Allele?
CYP2D6	*3	rs35742686	T	-	YES
	*4	rs3892097	C	T	YES
	*6	rs5030655	A	-	YES
	*7	rs5030867	T	G	YES
	*8	rs5030865	C	A	YES
	*9	rs5030656	CTT	-	YES
	*10, *4	rs1065852	C	T	YES
	*10	rs1135840	C	G	YES
	*12	rs5030862	C	T	YES
	*14	rs5030865	C	T	YES
	*15	rs774671100	A	-	YES
	*17	rs28371706	G	A	YES
	*19	rs72549353	AGTT	-	YES
	*29	rs59421388	G	A	YES
	*41	rs28371725	C	T	YES
	*56B	rs72549347	G	A	YES
	*59	rs79292917	C	T	YES
CYP3A5	*3	rs776746	T	C	YES
	*6	rs10264272	C	T	YES
	*7	rs41303343	A	-	YES
DPYD	*2A	rs3918290	C	G/T	YES
	*12	rs1057519962	G	A	YES
	*12	rs1057519962	G	T	YES
	*10	rs1801268	C	A	YES
	*7	rs72549309	ATGAATGA	ATGA	YES
	*8	rs1801266	G	A	YES
	*13	rs55886062	A	C/T	YES
	HapB3	rs75017182	G	C	YES
	HapB3	rs75017182	G	T	YES
	c.2846A > T	rs67376798	T	A	YES
	c.557A > G	rs115232898	T	C	YES
	HapB3 (tag)	rs56038477	C	T	YES
	c.680 + 139G > A	rs6668296	T	C	NO
HCP5	*HLA-B**57:01	rs2395029	T	G	YES [#2]
HCP5	*HLA-B**57:01	rs2395029	T	G	YES
IL28B		rs12979860	T	C	YES

Gene	Allele	SNP (rs)	Ancestral	Mutant	Defines Actionable [#1] Allele?
TPMT	*2	rs1800462	C	G	YES
	*3B, *3A	rs1800460	G	A	YES
	*3C, *3A	rs1142345	A	G	YES
	*4	rs1800584	C	T	YES
	*11	rs72552738	C	T	YES
REP TPMT	*2	rs1800462	C	G	YES
	*3B, *3A	rs1800460	G	A	YES
NUDT15	*3	rs116855232	C	T	YES
VKORC1	(−1639G > A)	rs9923231	C	T	YES
		rs9934438	G	A	NO
		rs7294	C	T	NO
UGT1A1	*6	rs4148323	G	A	YES
	*80	rs887829	C	T	YES [#3]
HLA-A3101		rs1061235	A	T	YES [#4]
SLCO1B1	*5	rs4149056	T	C	YES
	*1b	rs2306283	G	A	YES
	c.−910G > A	rs4149015	G	A	YES
	*2	rs56101265	T	C	YES
	*3	rs56061388	T	C	YES
	*6	rs55901008	T	C	YES
	*9	rs59502379	G	C	YES
	*10	rs56199088	A	G	YES
		rs11045879	T	C	NO
CYP1A2	*1C	rs2069514	G	A	NO
	*1F	rs762551	A	C	NO
	*1B	rs2470890	T	C	NO
CYP2A6	*9	rs28399433	A	C	NO
CYP2C8	*2	rs11572103	T	A	NO
	*3	rs10509681	T	C	NO
		rs11572080	C	T	NO
	*4	rs1058930	G	C	NO
CYP3A4	*3	rs4986910	A	G	NO
	*2	rs55785340	A	G	NO
	*6	rs4646438	T	TT	NO
	*18	rs28371759			NO
	*22	rs35599367	C	T	NO

Gene	Allele	SNP (rs)	Ancestral	Mutant	Defines Actionable [#1] Allele?
ABCB1	C3435T	rs1045642	C	T	NO
	G2677 T/A	rs2032582	C	A	NO
	G2677 T/A	rs2032582	C	T	NO
	C1236T	rs1128503	G	A	NO
TBL1Y (SEX)		rs768983			NO
ABCG2		rs2231142	G	T	NO
ABCC2		rs2273697	G	A	NO
COMT		rs4680	G	A	NO
		rs13306278	C	T	NO
OPRM1		rs1799971	A	G	NO
SLC22A1	*2	rs72552763	GAT	-	NO
	*3	rs12208357	C	T	NO
	*5	rs34059508	G	A	NO
UGT2B15		rs1902023	A	C	NO
RARG		rs2229774	G	A	NO
SCL28A3		rs7853758	G	A	NO
UGT1A4		rs2011425	T	A	NO
UGT1A4		rs2011425	T	G	NO
EPHX1		rs2234922	A	G	NO
		rs1051740	T	C	NO
MTHFR		rs1801133	G	A	NO
XPC		rs2228001	T	G	NO
ERCC1		rs11615	A	G	NO
ERCC1		rs3212986	A	C	NO
XRCC1		rs25487	C	T	NO

#[1]: The term “actionable allele” refers to variants related to, or defining alleles related to phenotypes potentially associated with a clinical recommendation issued by the Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Dutch Pharmacogenetics Working Group (DPWG). #[2]: The linkage disequilibrium (LD) between this variant and HLA-B*57:01 has been validated and may be used as a surrogate biomarker. #[3]: According to CPIC’s guideline on UGT1A1 and irinotecan, UGT1A1*80 is in very high LD with *28 and can be considered a surrogate marker. #[4]: This variant has been proposed as a surrogate biomarker for HLA-A*31:01 but requires LD validation.

3. Relevant Pharmacogenetic Tests

In 2009, IFNL3 genotype (IL28B) was found to be the best predictor of response to ribavirin (RBV) and pegylated interferon alpha (PEG-IFN-α) for the management of patients infected with hepatitis C virus Genotype 1 [22][23]. The first test in our pharmacogenetics unit for IFNL3 rs12979860 and rs8099917 was performed in March 2011. Initially, LightSNP probes designed by TIB Molbiol (Madrid, Spain) were used for qPCR genotyping in a LightCycler instrument (Roche Diagnostics, Barcelona, Spain) and since 2020, these SNPs are included in our Open Array customized array. Genotyping of this variant was initially a requirement of the Spanish Ministry of Health for prescribing telaprevir and boceprevir in combination with pegylated interferon and ribavirin in patients with a low likelihood of achieving a sustained viral response. A total of 792 patients were genotyped and the results were as follows: 266 of them carried the IFNL3

rs12979860 C/C genotype (33.6%), 409 the C/T genotype (51.6%) and 117 the T/T genotype (14.8%); 404 carried the rs8099917 T/T genotype (51.0%), 343 the G/T genotype (43.3%) and 45 the G/G genotype (5.7%). Currently, this test is rarely requested due to the disuse of these drugs in favor of direct antivirals.

The cytochrome P450 isoform 2C19 (CYP2C19) metabolizes several relevant drugs like antidepressants, protein pump inhibitors and clopidogrel, among others [24]. The polymorphism of this gene is related to phenotypic variability in CYP2C19-mediated metabolism. The first test was performed in our pharmacogenetic unit in June 2013. In our hospital, this test is mainly performed for the prevention of atherothrombotic and thromboembolic events in patients with carotid, vertebral or cranial artery stent implantations [25][26]. Since 2013, a total of 188 patients were genotyped for CYP2C19 *2, *3, and *17 and since 2020, for *4 , *5 , *6 , *7, *8 and *35, being the results as follows: 80 patients (42.6%) were NMs, 47 (25%) were rapid metabolizers (RM), 48 (25.5%) were IMs, 9 (4.8%) were ultrarapid metabolizers (UMs) and 4 (2.1%) were PMs (**Table 2**). Clopidogrel may not be used for IMs and PMs [27], therefore, for >27% of patients at risk for cardiovascular events, the drug was switched to prasugrel or ticagrelor. Additionally, our study associating the UM phenotype to bleeding risk [25] was well received by physicians at our hospital who, occasionally, also switched drugs for this phenotype.

Table 2. Prevalence of *CYP2C19* genotypes in a Spanish population.

Genotype	Count	%	Phenotype
***1/*1**	**80**	**42.6**	**NM**
***1/*17**	**47**	**25.0**	**RM**
***1/*2**	**39**	**20.7**	**IM**
***2/*17**	**9**	**4.8**	**IM**
***17/17**	**9**	**4.8**	**UM**
***2/*2**	**4**	**2.1**	**PM**
Total	**188**	**100**	

UM: ultrarapid metabolizer; RM: rapid metabolizer; NM: normal metabolizer; IM: intermediate metabolizer; PM: poor metabolizer

Meanwhile, CPIC's guideline on nonsteroidal anti-inflammatory drugs (NSAIDs) was published on March 2020 [28]. This meant that, for patients treated at the Pain Management Unit, two actionable pharmacogenetic tests were available from which they could benefit (CYP2C9 and CYP2D6 for NSAIDs and tramadol, respectively). This situation rendered obsolete the working procedure in which, for each patient, a specific pharmacogenetic test for a gene or drug was requested. Given our advances in genotyping technology and the greater pharmacogenetic knowledge available, lots of useful information were generated and not informed for the benefit of patients. Not only was important pharmacogenetic information related to their disease being generated, but a battery of pharmacogenes related to dozens of drugs and pathologies was also being genotyped. However, at this point, only individual gene-drug pairs were reported.

This motivated the establishment of the PriME-PGx initiative with two starting projects aimed at the expansion of clinical pharmacogenetics. The first one, the PROFILE project, in which specific pharmacogenetic profiles were created for specific therapeutic areas. Not only did this change the way pharmacogenetic results were reported, but also promoted the expansion of pharmacogenetic knowledge at our hospital. Briefly, instead of reporting individual gene-drug pairs, several of them were compiled in specific reports for each hospital department. The second one, the GENOTRIAL project, in which a report of clinically relevant pharmacogenetic findings is provided to any healthy volunteer consenting participation for pharmacogenetic research at the Clinical Trials Unit of Hospital Universitario de La Princesa (UECHUP). The PROFILE Project is described as follows:

4. The PROFILE Project

Actionable pharmacogenetic tests are nowadays directed to prescribers at the different Departments of our Hospital. Seven pharmacogenetic profiles were created based on the specific requirements of seven hospital departments. Briefly, they are described as follows:

- Pain Management (PMU) profile: this profile includes evident drug-gene associations for anti-inflammatory and analgesic drugs (e.g., tramadol-*CYP2D6* and NSAIDs-*CYP2C9*) and other less evident pairs: antidepressants, statins

or antiepileptic drugs.

- Oncology (ONC) profile: this profile includes evident drug-gene associations for antineoplastic drugs (e.g., DPYD and 5-fluorouracil, *CYP2D6* and tamoxifen or *UGT1A1* and irinotecan), immunosuppressants (e.g., *TPMT*/*NUDT15* for azathioprine and mercaptopurine and *CYP3A5* for tacrolimus) and other less evident pairs: tramadol, codeine, ondansetron or tropisetron.

- Neurology-psychiatry (NEU) profile: this profile includes evident drug-gene associations for antipsychotics (e.g., CYP2D6 and aripiprazole), selective serotonin reuptake inhibitors (SSRIs) (e.g., *CYP2D6* and fluvoxamine or *CYP2C19* and citalopram), tricyclic antidepressants (e.g., CYP2D6 and desipramine or CYP2C19 and imipramine), *CYP2C9*-siponimod and antiepileptic drugs (e.g., *HLA-B**15 and A*31 for carbamazepine).

- Immunosuppressants (IMS) profile: this profile includes associations for immunosuppressants exclusively (e.g., *TPMT/NUDT15* for azathioprine and mercaptopurine and *CYP3A5* for tacrolimus).

- Infectious Diseases (INF) profile: this profile includes evident drug-gene associations for anti-infectious agents (e.g., *HLA-B* for abacavir, *DPYD* for flucytosine, *IFNL3* for ribavirin or peg-α-2a/2b interferon, *UGT1A1* for atazanavir, *CYP2B6* for efavirenz and *CYP2C19* for voriconazole).

- Gastroenterology (DIG) profile: this profile includes an evident drug-gene association, i.e., *CYP2C19* and protein pump inhibitors (PPIs) (e.g., omeprazole) and other less evident drug-gene pairs (*CYP2C19*-clopidogrel, *TPMT/NUDT15* for azathioprine and mercaptopurine or *CYP2C9*, *CYP4F2* and *VKORC1* for warfarin and acenocumarol).

- Cardiovascular medicine (CAR) profile: this profile includes evident drug-gene associations for agents related to cardiovascular or blood function (e.g., *SLCO1B1* for statins or *CYP2C19* for clopidogrel and *CYP2C9*, *CYP4F2* and *VKORC1* for warfarin and acenocumarol) and other less evident drug-gene pairs (e.g., *CYP2C19*-PPIs).

As previously mentioned, the way pharmacogenetic tests were requested and communicated changed significantly. With the PROFILE project, the methodology was modernized. No more applications for pharmacogenetic tests were processed on written paper. Nowadays, the clinical record allows requesting pharmacogenetic tests electronically. Physicians can select pharmacogenetic profiles which contain the test they would like to request along with several other tests that are related to their medical specialty. Array genotyping allows designing a panel of relevant pharmacogenes which covers all of the pharmacogenetic profiles mentioned. Hence, information for all of these genes is obtained and can be used for the benefit of the patient. In addition, an alert system for relevant pharmacogenetic findings was implemented in patient's medical record, regardless the requested profile. For instance, should a physician request the CAR profile, a report in pdf format will be uploaded to their medical record with all relevant detailed pharmacogenetic information. Further, if any other relevant information is discovered, (e.g., the patient is a *DPYD* PM or carries the *HLA-B**57:01 allele), simplified alerts will be added to the patient's medical record, similar to an allergy alert (e.g., "*DPYD PM* alert: prescription of capecitabine and 5-fluorouracil"; *HLA-B*57:01* alert: do not prescribe abacavir).

It is worth noting that, since 2020, the Clinical Pharmacology Department offers a Pharmacogenetics consultation every Friday. This is aimed at polymedicated patients who require an individualized analysis of interactions and pharmacogenetic findings to minimize the toxicity of their pharmacotherapy and increase its effectiveness.

5. Conclusions and Future Perspective

Not only did we implement pharmacogenetic testing in our hospital, but we are actively participating in its implementation at regional and national level. This justifies the creation of the PriME-PGx initiative, a pioneer project in our country and in Europe. Our initiative initially promotes the PROFILE and GENOTRIAL projects, which will contribute in the short term to the expansion of pharmacogenetic knowledge among professionals, the general population and throughout the field of clinical trials.

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